Anterior Segment Seeding in Eyes With Retinoblastoma Failing to Respond to Intraophthalmic Artery Chemotherapy

Efthymia Pavlidou, MD; Christopher Burris, MD; Caroline Thaung, FRCPath; Irene Scheimberg, FRCPath; Judith Kingston, FRCP; John L. Hungerford, FRCS, FRCOphth; M. Ashwin Reddy, FRCOphth; Mandeep S. Sagoo, FRCS(Ed), FRCOphth

OBJECTIVES To describe clinicopathologic observations in eyes in which intraophthalmic artery chemotherapy for retinoblastoma failed and to report anterior chamber involvement.

OBSERVATIONS A retrospective case series of 12 enucleated eyes (11 patients) with retinoblastoma refractory to intraophthalmic artery chemotherapy between March 1, 2010, and October 31, 2013, at University College London Institute of Ophthalmology and the Retinoblastoma Service, Royal London Hospital. Data analysis was conducted from June 1, 2014, to March 1, 2015. The International Classification of Retinoblastoma groups were B in 1 eye (8%), C in 4 eyes (33%), and D in 7 eyes (58%). Systemic chemotherapy with vincristine sulfate, etoposide, and carboplatin had failed in 10 patients (91%) and 6 eyes (50%) received additional local treatments. In 6 eyes (50%) anterior chamber invasion was clinically detectable. On histopathologic examination, 4 eyes (33%) had no viable retinal tumor; the remainder had poorly differentiated tumor (6 eyes [50%]) or moderately differentiated tumor (2 eyes [17%]). Anterior segment involvement occurred in the ciliary body and/or ciliary muscle (7 eyes [58%]), iris (6 eyes [50%]), and cornea (4 eyes [33%]).

CONCLUSIONS AND RELEVANCE Intraophthalmic artery chemotherapy can fail in eyes with retinoblastoma. In contrast to previous reports on outcomes following intraophthalmic artery chemotherapy, our series shows involvement of the anterior segment of the eye, including the ciliary body, iris, and cornea. Careful case selection and follow-up are advised.

Published online September 3, 2015. doi:10.1001/jamaophthalmol.2015.2861
multiple sections through both calottes and a transverse section from the optic nerve at the surgical margin.

Results

A total of 12 eyes with retinoblastoma that had failed to respond to IAC were enucleated from 11 patients during the study period. There were 8 males and 4 females (6 left and 6 right eyes). The mean (median [range]) age at first diagnosis was 36 (12 [4-147]) months and, at the time of the first IAC treatment, 57 (39 [14-151]) months. The International Classification of Retinoblastoma7 group was B in 1 eye (8%), C in 4 eyes (33%), and D in 7 eyes (58%). A germline mutation was found in 6 of 11 patients (55%). Systemic chemotherapy, with a minimum of vincristine sulfate, etoposide, and carboplatin, was not effective in 10 patients (91%), and IAC was a secondary treatment; IAC was the primary treatment in only 1 case (9%).

Features requiring IAC included vitreous seeding in 11 eyes (92%), edge relapse in 6 eyes (50%), and multiple viable tumors in 1 eye (8%). All patients received IAC with single-agent melphalan hydrochloride, with successful catheterization of the ostium of the ophthalmic artery. The melphalan hydrochloride dose was 5.0 mg in 11 eyes (92%) and 10.0 mg in 1 eye (8%); the dose in another eye was increased from 5.0 mg to 7.5 mg after the second cycle. The number of cycles of IAC was 1 in 2 eyes (17%), 2 in 4 eyes (33%), 3 in 3 eyes (25%), 4 in 1 eye (8%), and 6 in 2 eyes (17%). Six of the 12 eyes (50%) received other treatments, including cryotherapy in 5 eyes (42%), laser ablation in 2 eyes (17%), external beam radiotherapy in 3 eyes (25%), and plaque brachytherapy in 4 eyes (33%). Clinical complications of IAC included third cranial nerve palsy (3 eyes [25%]), vitreous hemorrhage (4 eyes [33%]), iris neovascularization (1 eye [8%]), retinal pigment epithelial changes (2 eyes [17%]), retinal detachment (2 eyes [17%]), madarosis (1 eye [8%]), supratrochlear skin rash (2 eyes [17%]), and phthisis bulbi (1 eye [8%]).

Clinical indications (Figure 1 and Figure 2) for secondary enucleation were tumor viability and tumor seeding in the anterior segment in 6 eyes (50%), iris neovascularization in 6 eyes (50%), and neovascular glaucoma and vitreous hemorrhage in...
2 eyes each (17%). In 6 eyes (50%), involvement of the anterior chamber was apparent clinically, with tumor seeds floating in the anterior chamber and overlying the iris.

On histopathologic examination (Table and Figures 1 and 2), 4 of 12 eyes (33%) had no microscopic evidence of viable retinal tumors. In the remainder of the eyes, the retinoblastomas were graded as poorly (6 eyes [50%]) to moderately (2 eyes [17%]) differentiated.

Histopathologic involvement of the anterior segment was found in 8 of the 12 eyes (67%). This included eyes with involvement of the ciliary body and/or ciliary muscle (7 eyes [58%]), iris (6 eyes [50%]), and cornea (4 eyes [33%]). Three eyes (25%) had a small focus of tumor at the optic nerve head, but no tumors invaded the postlaminar optic nerve. No birefringent foreign material was found on polarization microscopy in any eyes. All cases with established high-risk retinoblastoma characteristics received adjuvant systemic chemotherapy.

Discussion

Intraophthalmic artery chemotherapy has received increasing attention since reports have shown good rates of tumor control and acceptable adverse effects. Persistent or recurrent viable vitreous or subretinal tumor seeds are the most difficult aspects of eye-preserving retinoblastoma therapy. Intraophthalmic artery chemotherapy offered control for 82% of the cases without subretinal seeds but only 64% to 67% for those with vitreous seeds. In the present series, we aim to contribute further to our understanding of treatment failure with IAC with the histopathologic findings of eyes with refractory retinoblastoma that required enucleation and demonstrate that anterior segment invasion occurred in 50% of the cases (6 eyes) on clinical grounds and 67% of the cases (8 eyes) on histopathologic analysis.

The indications for post-IAC enucleation are a combination of whether IAC was primary or secondary treatment, non-response, relapse, vitreous seeding, IAC complications, and threshold for enucleation. Persistence of vitreous seeds was the main reason for failure of eye preservation after IAC, which is in agreement with other reports. However, despite vitreous seeds described in those reports, anterior segment involvement was absent in contrast to our observations. In the present series, we also noted vitreous seeding but had the additional feature of tumor involvement of the ciliary body or muscle, iris, and cornea with active retinoblastoma in 67% of the cases (8 eyes). In fact, this situation has been reported previously after IAC in only 2 isolated cases; in one there was initial anterior chamber invasion that recurred and in the other involvement was documented on ultrasonographic biomicroscopy.

Vitreous seeds may persist after IAC for several reasons. The lack of vitreous blood flow and presence of blood-retinal barrier may prevent therapeutic IAC concentrations, but inactive vitreous seeds and drug resistance may also contribute. In one series, complete response after IAC was achieved in only 67% of the patients with vitreous seeds.
Seeding in Retinoblastoma After Failed Intraophthalmic Chemotherapy

ARTICLE INFORMATION
Submitted for Publication: March 28, 2015; final revision received June 22, 2015; accepted June 23, 2015.

Author Contributions: Drs Pavlidou and Sagoo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pavlidou, Burris, Reddy, Sagoo.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pavlidou, Burris, Sagoo.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Pavlidou.
Administrative, technical, or material support: Burris, Thaung, Hungerford, Reddy.
Study supervision: Burris, Reddy, Sagoo.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Previous Presentation: This study was presented in part at the 16th Biennial International Society of Ocular Oncology; September 30, 2013; Cleveland, Ohio.

REFERENCES